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PATENT APPLICATION
Docket No.: 0746.1024-006 (formerly UMMC91-03A2)

AF/1633
#47

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Harriet L. Robinson, Ellen F. Fynan, Robert G. Webster and Shan Lu		
Application No.:	08/187,879	Group:	1633
Filed:	January 27, 1994	Examiner:	Nguyen

For: IMMUNIZATION BY INOCULATION OF DNA TRANSCRIPTION UNIT

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REPLY BRIEF

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Brief on Appeal is submitted pursuant to the Examiner's Answer mailed from the United States Patent and Trademark Office (US PTO) on June 7, 2001.

The discussion presented herein is set forth under appropriate headings for the convenience of the Examiner.

Status of Claims

Claims 44-46, 50, 51, 62-64, 68-70, 74 and 78-89 are pending. Appellants' Attorney acknowledges with appreciation the Examiner's statements that Claims 62-64, 68-70, 74 and 78-80 are allowable, and the Examiner's statements that certain limited, proposed methods claims

are also allowable. Appellants' concerns regarding the proposed allowable claims which were declined, were focused primarily on the proposed methods claims. Appellants acknowledge the patentability of Claims 62-64, 68-70, 74 and 78-80, and will accept these allowable claims at the time when the remaining issues concerning the methods claims are resolved.

In view of these considerations, only Claims 44-46, 50, 51 and 81-89 are the subject of the appeal. These claims are drawn to methods of immunizing a mammal against an immunodeficiency virus of interest. As used in the application, "immunizing" refers to production of an immune response which protects either partially or totally from the manifestations of infection (i.e., disease) caused by the immunodeficiency virus. The methods include administering (by one or more of a variety of different routes) a DNA transcription unit comprising DNA encoding an antigen(s) of that immunodeficiency virus of interest (SIV or HIV), operatively linked to DNA which is a promoter region (which can be of retroviral origin or not of retroviral origin), wherein the mammal is protected from disease caused by that immunodeficiency virus of interest.

Issues

The Examiner's presentation of the issues is acknowledged. The enablement of the claims is at issue. The Examiner states that the issues are twofold:

> (i) whether the claimed invention is enabled for "a method of immunizing any SIV infectious mammal including humans against a simian immunodeficiency virus (SIV) comprising administering to the mammal a DNA transcription unit comprising a DNA encoding an antigen of said SIV by any administration route, whereby the mammal is protected from any disease by said SIV;" and
>
> (ii) whether the claimed invention is enabled for "a method of immunizing any HIV infectious mammal including humans against a human immunodeficiency virus (HIV) comprising administering to the mammal a DNA transcription unit comprising a DNA encoding an antigen of said HIV by any administration route, whereby the mammal is protected from any disease by said HIV."

This statement of the issues encompasses two issues set forth in Appellants' statement of the issues: in particular, whether the claims were enabled in breadth or should be limited to the

constructs taught by Appellants (issue (1) in the Brief on Appeal), and whether the claims were enabled in breadth or should be limited to the routes of administration demonstrated by Appellants or known in the art to be effective for DNA vaccination (issue (2) in the Brief on Appeal). The Examiner's Answer also appears to include a further issue: whether the claims were enabled in breadth for methods of "immunizing" "whereby the mammal is protected from disease" as set forth in the claims at issue, or whether the methods should be limited to a "method of reducing SIV or HIV infected cells." Appellants additionally set forth two other issues (issues (3) and (4) in the Brief on Appeal): whether it was clear whether protection was realized in the data presented; and whether the animal model used to generate the data was correlatable to a model for determining vaccination strategies. These two issues were addressed by the Examiner in the consideration of enablement of the claims, and thus appear to be "subset" issues of the Examiner's two issues as well as first two issues set forth by Appellants. Therefore, it appears that the Examiner and Appellants are in general agreement as to the remaining issues.

Discussion

The Claims have been rejected under 35 U.S.C. §112, first paragraph because the Examiner contends that the breadth of the claims is non-enabled and that the claims should be limited to constructs taught by Appellants, administered by multiple routes including the gene gun route. The Examiner further contends that the methods should be limited to a "method of reducing SIV or HIV infected cells" because the breadth of the phrase, "method of immunizing... whereby the mammal is protected from disease" as set forth in the claims at issue, is non-enabled.

To be enabling under 35 U.S.C. §112, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971).

In assessing enablement of a claimed invention, a variety of factors can be considered, including, for example, the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure (see, e.g., *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). The Examiner's Answer addresses several of these factors, each of which is similarly discussed below.

Breadth of Claims and Nature of Invention

As stated above, the claims at issue are drawn to methods of immunizing a mammal against an immunodeficiency virus of interest, wherein the immunodeficiency virus is either SIV or HIV, by administering a DNA transcription unit comprising DNA encoding an antigen of that immunodeficiency virus of interest, operatively linked to DNA which is a promoter region (which can be of retroviral origin or not of retroviral origin), wherein the mammal is protected from disease caused by that immunodeficiency virus of interest. The invention thus pertains to what is frequently termed in the art as "naked DNA" and its use in generating a particular immune response upon administration, e.g., "immunization." As described in the Specification at page 7, lines 5-8, "immunizing" as used in the claims refers to production of an immune response which protects, partially or totally, from the manifestations of infection (i.e., disease) caused by the infectious agent. Furthermore, immunizing can result in protection against infection, or infection to a lesser extent than would occur without immunization (page 7, lines 9-11). Thus, "immunizing" does not refer solely to protection against infection *per se* (although that is contemplated), but rather, refers also to generation of an immune response that lessens or eliminates manifestations of disease after infection with the infectious agent. The scope of these claims is commensurate with the scope of enablement provided by the application, as described in further detail below. One of ordinary skill in the art would be able to make DNA transcription units as described in the Specification and use them in the claimed methods, to "immunize" in accordance with the methods of the invention as set forth in the application.

Amount of Direction Provided by the Inventor, Working Examples, and Quality of Experimentation Needed Based on the Disclosure

DNA constructs and their preparation are described in detail in the Specification, particularly, for example, at p. 45, line 16 *et seq.* (Examples 11-15). Examples 11 and 13 describe methods for preparing constructs (both SIV-related and HIV-related), including specific constructs; Example 15 details how to clone additional sequences (e.g., *env* sequences) from patient isolates for use in preparation of additional constructs; and Example 12 describes testing of immunogenicity of the constructs. The specific constructs taught in the Specification are representative of those useful in the methods.

The Specification describes a wide variety of routes that are suitable for DNA vaccination in the methods of the invention (see, e.g., p. 9, lines 11-21). The success of several routes of administration of DNA constructs for DNA vaccination is established in the state of the art, as described in further detail below; furthermore, examples of such success in DNA immunization can be seen, for example, in Example 4 (page 22, line 19 *et seq.*), where immunization by intramuscular, intravenous, and a combination of routes (intramuscular, intravenous, and intraperitoneal) provided excellent protection after challenge with disease; immunization by intranasal (mucosal) route provided good protection after challenge with disease; and immunization by intradermal or subcutaneous routes provided protection after challenge with disease that was superior to the control immunizations. In addition, gene-gun delivered DNA to the epidermis provided excellent protection after challenge with disease (see Example 6, page 28, line 8 *et seq.*).

The use of such constructs, administered by a variety of routes, is described, for example, in Example 14, which sets forth how to conduct a vaccine trial to assess efficacy of the constructs. One of ordinary skill in the art, given these teachings of the Specification, would be able to assess the efficacy of any DNA transcription unit using such a vaccine trial. DNA constructs identified by such trials could then be used in the claimed methods. While preparation of DNA constructs, and performance of the vaccine trials, would take time and effort, the methods are described sufficiently such that one of ordinary skill in the art could do so without undue experimentation.

The results of a simian trial conducted in accordance with the teachings of Example 14, were described in the Declaration under 37 C.F.R. §1.132 of Dr. Harriet L. Robinson (the "Data Declaration," submitted on March 1, 1996). The results described in the Data Declaration were obtained not only with gene gun immunization but also with multiple-route immunization. The experiments described in the Data Declaration relate to assessment of the ability of a nucleic acid vaccine to protect against disease in a highly virulent, uncloned SIVmac251 rhesus macaque model. The virus used generally causes $\geq$ 50% incidence of AIDS during the first year of infection (see, e.g., description of the virulence of the particular virus in Lu, S. *et al.*, "Simian Immunodeficiency Virus DNA Vaccine Trial in Macaques," *J. Virol. 70(6)*:3978-3991 (1996), a copy of which was submitted previously). In the case of highly virulent models, partial protection, rather than complete protection, against disease is usually expected.

As described in the Data Declaration, administration of nucleic acid constructs comprising pJW4303 vectors containing sgp110(120) or sgp130(140), resulted in a more rapid reduction of viral loads to chronic levels in the immunized animals following the subsequent challenge with the virus, in comparison to the rate of reduction in control animals (reduction was achieved in half the time). The ability of the vaccinations to effect such a rapid reduction of viral loads was particularly noteworthy in view of the virulence of the challenge virus. If a less virulent challenge virus were used, one of ordinary skill in the art would reasonably expect that even greater protection (e.g., further reduction of viral loads or other protective immune responses) would be achieved. Furthermore, if a smaller amount of challenge virus were used (e.g., the amount of virus that would be present in a natural exposure, which is much smaller than the amount of virus used for the virus challenge during the vaccine trial), one of ordinary skill in the art would similarly reasonably expect that even greater protection would be achieved.

Thus, the data described in the Data Declaration do demonstrate immunizing and protection against disease, as those terms are used in the Specification and set forth in the claims at issue. As indicated above, "immunization" refers to production of an immune response which protects, *partially or totally*, from the *manifestations of infection* (i.e., disease) caused by the infectious agent, and can result in protection against infection, or infection to a lesser extent than would occur without immunization. Thus, "immunizing" includes generation of an immune response that *lessens or eliminates* manifestations of disease when infection with the infectious

agent occurs after immunization. Immunization that causes a rapid reduction in viral load (e.g., a reduction of viral load to the chronic level in 6 weeks instead of the average 12 weeks, as described in the Data Declaration) is consistent with the generation of an immune response that lessens manifestation of disease upon infection, and thus demonstrates "immunizing" as the term is described in the Specification. Thus, the application is clearly enabled for "immunizing" of an animal against manifestations of infection.

The State of the Prior Art, the Level of One of Ordinary Skill, and The Level of Predictability in the Art

The Examiner cites several references in the discussion of the state of art and level of predictability in the art. These are addressed under headings appropriate for the subject matter to which the reference pertains.

Animal Model

In relation to the animal model used in the experiments described above, the Examiner cites a discussion of animal models by Haynes (*Science* 260:1279-1286 (1993)), emphasizing that "no animal model exactly mirrors human HIV infection" and that "the immune correlates of protection against HIV are not known" (pp. 12 and 14 of Examiner's Answer). It is noteworthy that this Haynes reference does not mention DNA constructs as a type of experimental immunogen for HIV vaccine development (see, e.g., Table 2). Although the Haynes reference does indicate that direct immunization with complementary DNAs of HIV proteins has been contemplated, such DNAs are a teaching away from the current invention. Complementary DNAs are designed to inactivate HIV DNA by binding of the complementary DNAs to HIV DNA. In contrast, the DNA constructs of the current invention are designed to be expressed in the individual, thereby generating an immune response. Thus, the teachings of Haynes are not applicable to current invention.

Assuming, however, that the issue remains of whether an appropriate model exists and has been used in the experiments described above, there are, in fact, animal models which are useful for study of vaccine candidates for SIV/HIV, without being an "exact mirror" of human HIV infection. The references cited by Appellants (i.e., Gardner, M.B., *Antiviral. Res.* *15*:267-

286 (1991); Gardner, M.B., *Dev. Biol. Stand.* *72*:259-266 (1990); Johnson, P.R. and Hirsch, V.M., *Int. Rev. Immunol.* *8*:55-63 (1992); and McClure, H.M. *et al., Ann. NY Acad. Sci.* *616*:287-298 (1990)) were selected, in part, because they demonstrate the state of the art at the time the application was filed; they were further selected because of statements concerning the use of the models in development of vaccines. For example, the Gardner (1991) reference states:

> Animal lentivirus infections provide a valuable resource for understanding mechanisms of pathogenesis and for development of effective antiviral drugs and *vaccines* with direct relevance to HIV and AIDS (p. 268, Introduction, citations omitted and emphasis added).

This Gardner reference goes on to describe vaccine trials in the macaque model system (see page 269 *et seq.*). Thus, this Gardner reference clearly sets forth that animal lentivirus infections, such as SIV infection in macaques, are useful for development of vaccines, as exemplified by several studies using the SIV macaque model for vaccine trials.

As another example, the McClure reference states in its introduction:

> The magnitude and continuing growth of the current worldwide AIDS pandemic make the development of effective vaccines and antiviral drugs of utmost urgency. These efforts, especially studies of the pathogenesis of retroviral infections and testing of antiretroviral drugs, immune system modulators, and *vaccines* will be greatly facilitated by access to appropriate animal models. The SIV-infected nonhuman primate has been established as an excellent animal model system for conducting such studies. (p. 287, Introduction; citations omitted and emphasis added.)

Thus, the McClure reference specifically states that SIV-infected nonhuman primates are an excellent animal model system for studies which include studies of vaccines.

In view of these considerations, it is clear that appropriate models exist and are accepted by those of ordinary skill in the art as being predictive not only for SIV infection in primates but also for HIV infection in humans, even though the Haynes references states that there may not be any one model that "exactly mirrors" human immunodeficiency virus infection.

Routes of DNA Vaccination

The Examiner states that the state of the art of DNA vaccination remained unpredictable at the time the invention was made, in relation to the route of administration of the DNA, and

cites Tang *et al.* (*Nature* 356:152-154 (1992)) as indicating that gene gun administration of antigen generated antibody responses, but that injection with a hypodermic needle did not (p. 13 of Examiner's Answer). However, Appellants' own specification has demonstrated that a wide variety of routes of administration can be used to generate an immune response through DNA vaccination. In addition, relevant art references indicate that a wide variety of routes can be utilized for DNA vaccination. For example, Pardoll and Beckereig (*Immunity* 3:165-169 (1995), a copy of which was submitted previously as reference AY2 on the Information Disclosure Statement) state that:

> It is now well established that injection of naked DNA through any of a number or routes reproducibly induces both humoral and cellular immune responses against the encoded antigens (p. 167).

Thus, Appellants' specification, as well as the state of the art of DNA vaccination at the time of the invention, demonstrates that a wide variety of routes of administration are known in the art to be useful for DNA vaccination.

Predictability of Protective Response

The Examiner states that, due to the complexity of the immune responses in generating a protective response against any HIV strain in any mammal including humans, it is unpredictable whether a simulation of an HIV-specific antibody response, correlatable to the SIV working models used, would result in any protective immune response (p. 15 of Examiner's Answer). The Examiner cites Hoffenbach *et al.* (*J. Immunology* 142(2):452-462 (1989)), as stating that "no clear correlation exists at present between the presence of HIV-specific CTL and resistance to progression toward AIDS," and further cites Butini *et al.* (*J. Cellular Biochemistry* Suppl. 18B:147, abstract J306 (1994)), as demonstrating that a patient with high HIV-specific CTL activity had rapidly progressive disease, while a patient with no CTL activity had no progression of immunodeficiency disease (p. 15, Examiner's Answer.) The Examiner additionally cites Kuby (*Immunology*, W.H. Freeman and Company, New York (1992)), as stating that "the presence of high titers of circulating antibody to HIV proteins in no way indicates protective immunity" (p. 18, Examiner's Answer).

The Hoffenbach *et al.* and the Butini *et al.* references cited by the Examiner describe investigation of HIV-specific CTL activity in humans infected with the HIV virus. Hoffenbach *et al.* describe high frequency of HIV-specific cytotoxic T lymphocytes (CTL). The quantities of CTL and CTL precursors decreased over time as the clinical and immunological status of the infected individuals deteriorated. Butini *et al.* describe high CTL activity in a patient with rapidly progressive disease; no CTL activity in a patient with no progression of disease; and moderate CTL activity in a patient with slowly progressive disease.

These data differ in their conclusions regarding the relationship between CTL response to an antigen and protection against disease. However, Hoffenbach *et al.* and Butini *et al.* utilize very small samples, drawing into question whether any conclusions can be drawn from these references concerning the relationship between CTL response to HIV and progression of disease and even whether they can be considered representative of the state of the art concerning relationships between CTL response and protection against disease. Furthermore, it should be noted that Appellants are not claiming a specific CTL or antibody response; rather, the claims are drawn to immunization and protection against manifestations of infection, as described and defined above. It is not necessary to demonstrate stimulation of antibody formation, or CTL activity, in order to have a protective effect, as cytotoxic T lymphocytes are not always a necessary component for protective effect. Furthermore, it has been demonstrated that even DNA vaccinations which raise low to undetectable titers of antibody can confer protection against disease (see, e.g., the Specification at page 30 *et seq.*) While CTL or antibody response may be an indication of the presence of such an immune response, it is not determinative. What is required by the claimed invention is not that a particular mechanism or type of immune response be generated, but rather, that the immune response which is generated by the DNA vaccine, protects, partially or totally, from the manifestations of infection (i.e., disease) caused by the infectious agent. As discussed above, Appellants have demonstrated successful protection against manifestations of disease.

The Examiner additionally cites Glaser (*Genetic Engineering News* 6 (Jan. 1, 1996), stating that a variety of obstacles continue to challenge researchers and clinicians in the development of vaccines for HIV, including the need to induce several types of immunity; latent HIV residing in immunoprivileged sites; and a lack of a good animal model. The animal model

is discussed above. In addition, as discussed above, it is not the type of immunity that is induced, but rather, the ability of the immune response (whatever the type of response may be) to protect partially or totally against manifestations of disease. For example, even if latent HIV were to reside in immunoprivileged sites following infection, partial protection (e.g., immunization that causes a rapid reduction in viral load, such as that described in the Data Declaration) would still be possible, thus allowing generation of an immune response that lessens manifestation of disease and demonstrating "immunizing" as the term is described in the Specification.

The Examiner further cites additional references concerning the variability of HIV antigen, including Rekosh *et al.* (*PNAS USA* 85:34-338 (1988)), Weiss (The Washington Post, *Genetic Vaccine Keeps Chimps Protected Against AIDS Virus*, p. A2, 4/30/1997), and Cohen and Fauci (JAMA 280(1):87-88 (1998)) stating that these references emphasize problems relating to genetic variability of HIV antigens and its impact on development of an AIDS vaccine (pp. 16-19, Examiner's Answer). These references, like many of the others described above, point out the difficulties associated with development of a vaccine targeting HIV. Rather than detracting from the claimed invention, however, these references serve to emphasize the importance of Appellants' invention. Appellants have, for the first time, demonstrated that immunization of a mammal by administering to the mammal a DNA transcription unit comprising a DNA encoding an antigen of SIV, whereby the mammal was protected at least partially from the manifestations of disease caused by the SIV, is indeed possible.

Furthermore, the breakthrough nature of Appellants' invention overcomes several concerns whether such a vaccine would be possible, such as questions regarding identification of which regions of the protein of interest were necessary for virus neutralization (e.g., as described by Rekosh *et al.* in relation to env protein). Appellants utilized DNA constructs which encoded env and pol antigens, without determining precisely which regions of these proteins were involved in generation of the immune response. In addition, the Specification addresses concerns regarding genetic variability of HIV antigens, as it describes in detail the methods of cloning of a variety of relevant sequences (see Example 15 at page 57 *et seq.*), and indicates that antigens from different subgroups or subtypes of the infectious agent, or different structural forms of the antigenic proteins, can be used in a mixture for a DNA vaccine (see p. 9, line 30 *et seq.*; p. 10,

line 22, through p. 13, line 20). These considerations can overcome many of the problems mentioned in the references cited by the Examiner.

Summary

In an analysis of the factors for enablement, the conclusion of enablement must be based upon the evidence as a whole (see *In re Wands*, *supra*). Appellants have provided ample guidance in the Specification to make the constructs of the invention, how to determine their efficacy, and how to use them in methods of "immunization" such that an immune response that lessens or eliminates manifestations of disease is generated when infection with the infectious agent occurs after administration of the constructs. Furthermore, Appellants have demonstrated successful immunization, as that term is defined and used in the Specification, in a relevant animal model for immunodeficiency virus. The relevant art as well as Appellants' Specification demonstrate that a variety of routes of administration of DNA constructs can be used with reasonable expectation of success. Given the correlation of the results in the animal model of SIV, to HIV infection in humans, as described above, one of ordinary skill would reasonably believe that an immune response which protects, partially or totally, from the manifestations of infection with SIV in primates, would similarly protect, partially or totally, from the manifestations of infection with HIV in humans. In addition, Appellants' Specification provides means to address concerns in the art regarding the variability of HIV antigens. Taking these considerations as a whole, the Specification, at the time the application was filed, teaches one of ordinary skill in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

Conclusion

In view of the discussion presented above, a variety of nucleic acid constructs, including the very specific constructs set forth in the composition claims, are enabled by the Specification, as are several different modes of administration of the constructs and use of the constructs in the methods of the invention. Furthermore, the data previously presented demonstrates a protective response that was obtained in a well accepted animal model. Therefore, it is respectfully requested that the rejections be reversed and that the claims be allowed.

If the Examiner believes that a telephone conversation would expedite prosecution, the Examiner is invited to contact Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to contact David E. Brook at (781) 861-6240.

Respectfully submitted,
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Drew M. Hoyle Reg. No. 36,361 for
Elizabeth W. Mata
Registration No. 38,236
Telephone: (915) 845-3558
Facsimile: (915) 845-3237

Lexington, MA 02421-4799
Date: August 7, 2001